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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	11

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/863,179	DURING ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *20-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☒ Claim(s) *1-11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/5/01* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7 and 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed November 26, 2001 (Paper No. 5) has been entered.

The response filed January 17, 2003 (Paper No. 10) has been entered. Applicant's election with traverse of Group I, Claims 1-19 in Paper No. 9 is acknowledged. The elected invention is drawn to a method of treating Parkinson's disease. The traversal is on the ground(s) that the broad unifying concept of the invention that is reiterated in all the claims is that of using a nucleic acid sequence encoding glutamic acid decarboxylase (GAD) that is delivered to target cells of the central nervous system and expressing the GAD protein to reduce a neurodegenerative disease. Applicants argue that cells involved in any number of neurodegenerative diseases would be targeted and that even though the different diseases produce different effects, all the cells in the central nervous system involved in the disease have the GAD receptor and therefore can be treated by expressing the GAD protein. Applicants assert that a single search would suffice. This is not found persuasive because a search for a method of treating Parkinson's disease with a GAD-expressing vector would not be considered a comprehensive search for a method of treating Alzheimer's disease with a GAD-expressing vector, and vice versa. A method of treating Alzheimer's disease would not be considered obvious over a method of treating Parkinson's disease. Therefore, additional searching would be required to cover a method of treating Alzheimer's disease. Thus, the searches would not be coextensive and therefore a search and examination of all 6 inventions in a single application would constitute a serious burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-25 are pending in the instant application.

Claims 20-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Applicant timely traversed the restriction requirement in Paper No. 10.

Accordingly, Claims 1-19 are examined herein.

Drawings

The drawings are objected to for the reasons set forth on the attached PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Claim Objections

Claims 1-11 are objected to because of the following informalities: The claims encompass non-elected subject matter, which should be deleted from the claims. The claims cover treatment of diseases other than Parkinson's disease. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating Parkinson's disease by administering to the subthalamic nucleus (STN) an rAAV vector comprising a nucleotide sequence encoding glutamic acid decarboxylase (GAD), wherein a symptom of Parkinson's disease is ameliorated, does not reasonably provide enablement for the use of any type of vector for the treatment of Parkinson's disease, nor for any target tissue other than the STN. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

Nature of the invention and breadth of the claims. The claims are directed to a method for treating Parkinson's disease by administering a vector comprising a nucleotide sequence encoding GAD. Thus, the claims are directed to gene therapy. The claims encompass the use of any type of vector comprising a GAD gene, any route of administration, and administration to any region of the brain, with some claims reciting specific regions. The specification contemplates using a wide variety of vectors to

achieve a therapeutic effect. It is well-established that the specification must teach how to use the claimed method over the full scope.

Amount of direction or guidance presented and presence or absence of working examples.

The specification fails to provide an enabling disclosure for methods of treating Parkinson's disease using the broad scope of vectors contemplated, with any route of administration, to any region of the brain, because the specification does not adequately teach how to use the claimed methods over such a broad scope to produce a therapeutic effect. The specification provides working examples demonstrating that administration of an rAAV vector encoding GAD significantly improves clinical deficits associated with Parkinson's disease in an animal model (the 6-OHDA lesion model). However, the specification does not provide specific guidance with regard to the use of other types of vectors or for administration to regions of the brain other than the subthalamic nucleus. With regard to the use of other types of vectors, the specification only provides general guidance. In an unpredictable art, specific guidance rather than general guidance is required. For the reasons discussed herein below, the gene therapy art is highly unpredictable.

State of the prior art and level of predictability in the art. The specification does not teach how to use the broad scope of vectors covered in the claims therapeutically for the following reasons.

Gene therapy is not routinely successful. Therefore, the disclosure itself must provide the necessary teachings with regard to how to carry out the claimed method to achieve a therapeutic effect. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). Orkin and Motulsky also point out that "[t]he types of diseases

under consideration for gene therapy are diverse; hence, many different treatment strategies are being investigated, each with its own set of scientific and clinical challenges" (page 1, paragraph 2). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). The instant specification does not adequately teach one skilled in the art how to use vectors other than rAAV vectors to achieve a therapeutic effect in the treatment of Parkinson's disease. Thus, absent evidence that the claimed methods can be used over the full scope in gene therapy applications to produce a therapeutic effect in an immunocompetent animal, such as a human or appropriate animal model, claims that encompass the use of vectors other than rAAV vectors are not enabled by the disclosure.

The specification fails to provide an enabling disclosure for targeting appropriate cells for the treatment of the diseases referred to in the specification. The specification contemplates using a wide variety of types of vectors. Only general guidance is offered with regard to delivering vectors other than rAAV to the appropriate site. However, the art recognizes that targeting strategies are not currently sufficient to overcome the problems known in the art. More importantly, the disclosure does not offer a solution to this problem. While progress has been made in recent years for *in vivo* gene transfer, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings in the art. For example, Miller et al. (1995) review the types of vectors available for *in vivo* gene therapy, and conclude that "for long-term success as well as the widespread applicability of human gene therapy, there will have to be advances ... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly

efficient delivery systems" (page 198, column 1). Deonarain et al. (1998) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain et al. review new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) review vectors known in the art for use in gene therapy and discuss problems associated with each type of vector. The teachings of Verma et al. indicate that a resolution to vector targeting has not been achieved in the art (see entire article). Verma et al. also teach that appropriate regulatory elements may improve expression, but that it is unpredictable which tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal et al. (1995) also review various vectors known in the art and indicate that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

In an article published after the effective filing date of the instant application, Rubanyi (2001) teaches that the problems described above remain unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far ..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially the section under "3. Technical hurdles to be overcome in the future", pp. 116-125).

Beyond the technical barriers to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claimed methods encompass the use of a wide variety of vector types to treat Parkinson's disease. While other

vector types may prove useful in the treatment of other diseases, their uses may be limited by the specific effects sought to be achieved. Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic (p. 131, paragraph 4). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (p. 113, paragraph 4). As of the filing date of the instant application however, even the most promising areas presented barriers to successful gene therapy that could not be overcome by routine experimentation.

The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al., p. 1789, column 1, paragraph 1). Rather, the prior art shows that intensive investigation has met with limited success.

Relative level of skill of those in the art and quantity of experimentation necessary. Although the level of skill in the art is high, given the high degree of unpredictability in the gene therapy art, the skilled artisan would be required to engage in intensive investigation, rather than routine experimentation to develop a therapeutic protocols that use vectors other than rAAV vectors. In view of the quantity of experimentation necessary to determine appropriate parameters for using the claimed methods therapeutically, and given the limited applicable working examples demonstrating an *in vivo* therapeutic effect for Parkinson's disease, the limited guidance in the specification, the broad scope of the claims with regard to the vectors and tissue targets, and the unpredictability in the gene therapy art, undue experimentation would have been required for one skilled in the art to practice the claimed methods over the full scope, using vectors other than rAAV and targeting tissues other than STN.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-19 are indefinite in their recitation of "expressing the GAD in the region of the brain an amount effective" because it appears that the phrase should read "**in** an amount effective."

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, William Phillips, whose telephone number is (703) 305-3388.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER